Clinical and pathological parameters predicting pathologic complete response after neoadjuvant chemoradiotherapy for locally advanced rectal cancer

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Objective
The aim of this study is to identify possible clinical predictors of complete response after neoadjuvant treatment in locally advanced rectal cancer (LARC) patients.
Background
Preoperative chemoradiotherapy (CRT) followed by total mesorectal excision and postoperative adjuvant chemotherapy for LARC is the standard of care with a local recurrence rate of only 5–10%.
On the other hand, various people react differently to neoadjuvant CRT. Neoadjuvant CRT is well received by the majority of patients, with a pathologic complete response (pCR) occurring in 10–30% of cases.
Predicting the response to neoadjuvant CRT is crucial from a clinical standpoint, since patients with pCR have a better prognosis and may require a different treatment plan than patients without pCR.
As a result, predicting pCR following neoadjuvant CRT for rectal cancer continues to be extremely useful for treating physicians.
To identify the clinical and pathological variables linked to a full response to preoperative CRT for rectal cancer, we assessed a group of patients with pCR in this study.
Patients and methods
The study included 153 patients with LARC that were enrolled in the study based on specific inclusion and exclusion criteria. Patients were treated by standard neoadjuvant therapy. Surgical resection was planned for 6–8 weeks after the completion of neoadjuvant CRT, irrespective of the response to CRT.
Pathological examination was performed to assess pathological response in the resected specimen. pCR was defined as the absence of viable tumor cells in the surgical specimen, including lymph nodes.
Results
After neoadjuvant chemoradiation, the pCR rate for rectal cancer patients was 20.8%; patients were split into pCR and non-pCR groups. Age, sex, BMI, performance score, tumor stage, tumor differentiation, tumor location, and surgical method were all evenly distributed across the two groups. The results of the multivariate analysis showed that pretreatment lymph node status, tumor size, and a carcinoembryonic antigen level of less than or equal to 5 ng/ml were independent risk factors of an elevated likelihood of pCR, as was an interval of more than or equal to 8 weeks between the completion of chemoradiation and treatment.
Conclusion
The pCR in rectal cancer following neoadjuvant chemoradiation is predicted by pretreatment carcinoembryonic antigen level of less than or equal to 5 ng/ml, an interval of more than or equal to 8 weeks between the end of chemoradiation and surgical resection, tumor size greater than 5 cm, and pretreatment lymph node status. By utilizing these predictive variables, we are able to forecast patients' outcomes and create flexible treatment plans. In certain, very specific situations, a wait-and-see policy might be appropriate.

Keywords:
locally advanced rectal cancer, neoadjuvant chemoradiotherapy, pathological complete response

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Introduction

In the United States, colorectal cancer ranks third in terms of both incidence and mortality from cancer among men and women [1].

Locally advanced rectal cancer (LARC) is defined as stage II (T3–T4, node negative) or stage III (node positive) disease. According to the guidelines of the National Comprehensive Cancer Network, patients with LARC should get trimodality treatment consisting of adjuvant chemotherapy, neoadjuvant chemoradiotherapy (CRT), and surgical resection with total mesorectal excision. Pelvic local recurrence has decreased significantly as a result, from 25% to roughly 5–10%. The rate of sphincter preservation can also be increased by neoadjuvant chemotherapy and radiation therapy [2–7].

On the other hand, various people react differently to neoadjuvant CRT. The majority of patients react to neoadjuvant chemotherapy, and between 10 and 30% of patients experience a pathologic complete response (pCR), in which the final surgical specimen has no live tumor cells. Some patients, meanwhile, do not respond to CRT or are resistant to it [3,4].

It has been demonstrated that patients with pCR had superior long-term results than those lacking pCR. Furthermore, a wait-and-see approach is both reasonable and safe for patients who have a clinically complete response to neoadjuvant CRT [6,8] From a therapeutic perspective, predicting the response to neoadjuvant CRT is critical because patients with pCR have a better prognosis and could need a different treatment strategy than those without pCR.

What precisely influences a patient's response to neoadjuvant CRT for rectal cancer is unknown, though. The carcinoembryonic antigen (CEA) level and tumor size are two of the clinical indicators that predict the tumor response to preoperative CRT, according to a number of small retrospective studies [9–11].

As a result, predicting pCR following neoadjuvant CRT for rectal cancer continues to be extremely difficult. To identify the clinical and pathological variables linked to a full response to preoperative CRT for rectal cancer, we assessed a group of patients with pCR in this study.

Patients and methods

This study was randomized prospective trial conducted between February 2020 and April 2023, on 153 patients with LARC that were enrolled in the study based on specific inclusion and exclusion criteria. Eligibility criteria included age 18–75 years, histopathologically confirmed rectal adenocarcinoma, with the inferior margin of the tumor less than 12 cm from the anal verge and clinical stage II (T3–T4, N0) or stage III (any T, N +ve).

Exclusion criteria

(1) Recurrent or metastatic disease.
(2) A history of malignant tumor or relapse.
(3) Cases managed by a watch-and-wait strategy after neoadjuvant CRT.

After approval of the protocol by Alexandria Faculty of Medicine ethics committee, all patients were informed well about all the procedures done through the study and they all signed an informed consent before being enrolled in the study.

Pretreatment evaluation

All patients in the present study were subjected to the following:

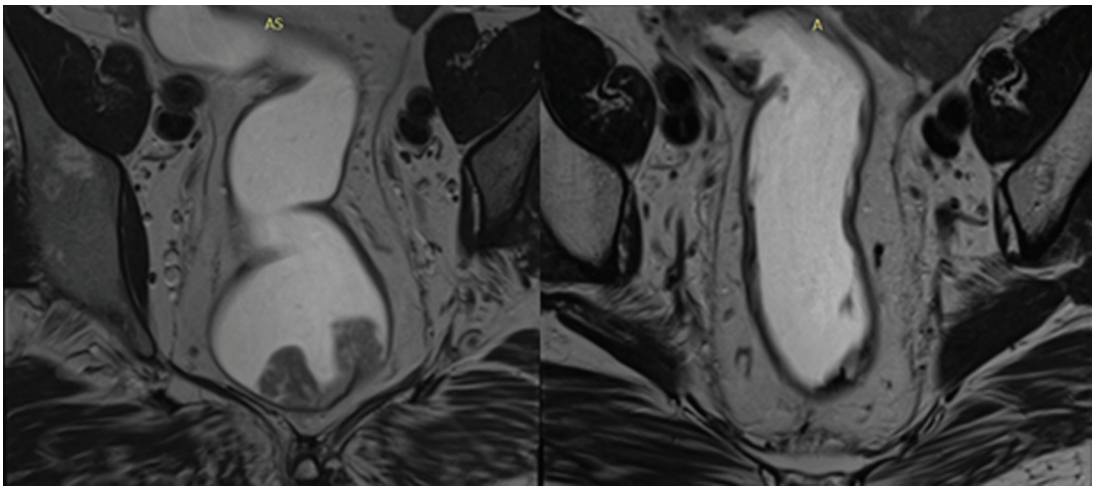
(1) Collection of demographic information included age, sex, and comorbidities.
(2) History taking with special emphasis on complaint, duration of complaint, previous anal surgeries, and other gastrointestinal complaints if present.
(3) Physical examination included abdominal and anorectal examination.
(4) Performance status assessment by using ECOG score for cancer patients [9] and calculation of BMI.
(5) Computed tomography of the chest, abdomen, and pelvis for staging.
(6) High-resolution thin slice (3 mm) pelvic MRI scans.
(7) Laboratory investigations included CEA measurement.
(8) Colonoscopy to confirm the diagnosis of adenocarcinoma.

Treatment

Patients received standard neoadjuvant therapy, which included concurrent CRT in the form of 45 Gy/25 fractions of radiation therapy, followed by a boost of 5.4 Gy/3 fractions with a concurrent bolus of 5-flurouracil+calcium leucovorin for the first 4 days, and capecitabine at 825 mg/m^2 twice daily for the final 3 days of radiation therapy (Fig. 1).

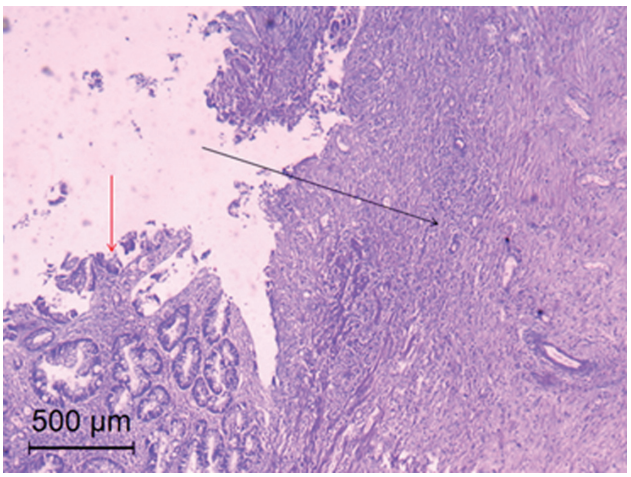
At least 6 weeks following neoadjuvant treatment, all patients underwent a reevaluation, which included high-resolution pelvic MRI, rigid proctoscopy, and DRE (Fig. 2).

Figure 1



Pelvic MRI before and after TNT (complete response).

Figure 2



Red arrow showing normal rectal muosa, black arrow showing tumor bed with inflammation and fibrosis and absence of tumor cells (complete pathological response).

Surgical resection was scheduled for 6–8 weeks following the end of neoadjuvant chemotherapy and radiation, regardless of the CRT response.

Surgery and pathology

Radical complete mesorectal excision (total mesorectal excision) was performed on each patient. The surgeon had the last say over the surgical procedure (i.e. anterior resection or abdominoperineal surgery). Sharp dissection under direct visualization through the appropriate pelvic facial planes was used for all procedures. For patients receiving ultra-low anterior resection, a diverting loop ileostomy was performed.

To evaluate the pathological response in the removed specimen based on the Mandard tumor regression grade, a pathological examination was conducted [10]. The lack of viable tumor cells, including lymph nodes, in the operative samples was referred to as pCR (Fig. 3).

Statistical analysis of the data

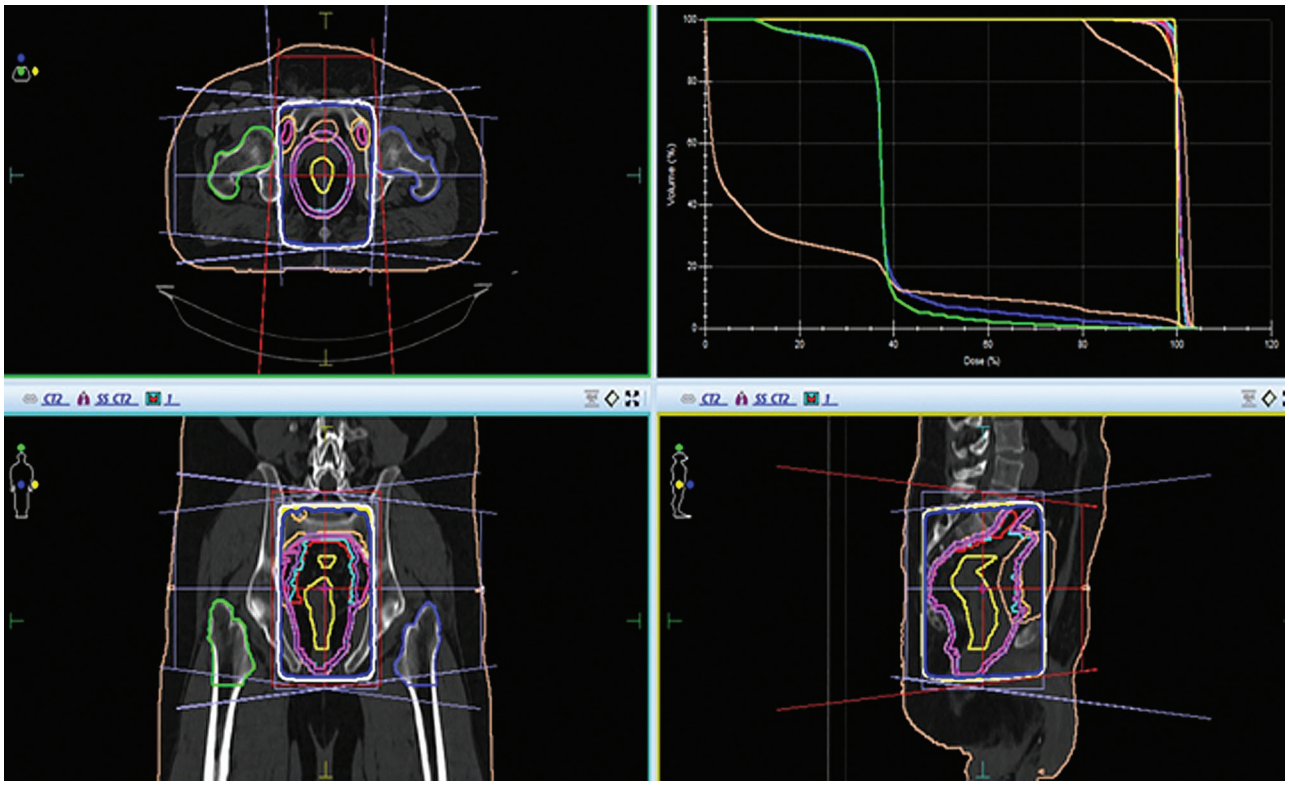
Data were fed to the computer and analyzed using IBM SPSS software package, version 20.0. (IBM Corp., Armonk, New York, USA). Categorical data were represented as numbers and percentages. χ^2 test was applied to investigate the association between the categorical variables. Alternatively, Monte Carlo correction test was applied when more than 20% of the cells have expected count less than 5. For continuous data, they were tested for normality by the Shapiro–Wilk test. Quantitative data were expressed as range (minimum and maximum), mean, and SD, median. Student t test was used to compare two groups for normally distributed quantitative variables. On the other hand, Mann–Whitney test was used to compare two groups for not normally distributed quantitative variables. Logistic regression to detect the most independent predictors for pCR. Significance of the obtained results was judged at the 5% level.

Results

The study included 64 (41.8%) women and 89 (58.2%) men, their ages ranged between 26 and 77 years, with a median of 52 years for the pCR group and 55 for non-pCR group (Table 1).

The CEA level was high in seven (20%) of 35 patients of the pCR group and 62 (52.5%) of 118 patients of the non-pCR group. The difference between the two groups was statistically significant (P=0.005) (Table 2).

Figure 3



Representative treatment plan for locally advanced rectal cancer with IMRT.

Out of the 153 patients, 118 (77.2%) did not have a pCR, and 35 (22.8%) did. The patients were split up into two groups: those with pCR (n=35) and those without pCR (n=118).

There was no statistically significant difference found in the age, sex, BMI, performance status, tumor stage, tumor differentiation, tumor site, or surgical procedure between the two groups.

The median interval between the completion of neoadjuvant CRT and surgery was significantly longer in the pCR group than in the non-pCR group (58 vs. 50 days, P<0.001).

The logistic regression analysis was done for the total sample (35 patients with no tumor residual vs. 118 patients with tumor residual) to determine the different parameters predicting pCR (Table 2).

On multivariate analysis, a pretreatment CEA level of less than or equal to 5 ng/ml [odds ratio (OR)=6.888, 95% confidence interval (CI)=1.662–28.551, P=0.008] and an interval from the completion of neoadjuvant CRT to surgery of more than or equal to 7 weeks (OR=39.413, 95% CI=8.892–174.700, P≤0.001), cN category (OR=0.101, 95% CI=0.025–0.412, P=0.001), and tumor size less than or equal to 5 cm (OR=6.176, 95% CI=2.110–18.080, P=0.001) were identified as independent predictors for achieving a pCR (Table 3).

Discussion

Neoadjuvant, CRT and surgery are the usual treatments for rectal cancer in clinical stages II and III. Neoadjuvant CRT enhances local control when compared to either postoperative CRT or surgical resection alone [2]. Significant morbidity and a roughly 4% 90-day death risk are associated with radical resection. It also has chronic functional urinary and gastrointestinal problems [11]. Patients who attained pCR have a history of improved survival, reduced rates of distant metastases, and higher rates of local control [6]. A number of research works have reported on a variety of helpful prognostic markers for pCR, including tumor size, preoperative CEA level, cell differentiation, and clinical T and N stages [12–14].

Developing a rectal cancer treatment plan may result from an understanding of these variables. Instead of

Table 1 Comparison between the two studied groups according to different parameters

	Total (*N*=153)	pCR (*N*=35)	Non-pCR (*N*=118)	Test of significance	*P*
Age (years)					
Median (minimum–maximum)	54 (26–77)	52 (26–73)	55 (26–77)	*t*=1.099	0.274
Mean±SD	52.73±12.16	50.74±12.27	53.31±12.12		
Sex [*n* (%)]					
Male	89 (58.2)	19 (54.3)	70 (59.3)	χ^2=0.281	0.596
Female	64 (41.8)	16 (45.7)	48 (40.7)		
BMI (kg/m^2)					
Median (minimum–maximum)	25 (17–34)	24 (18–33)	25 (17–34)	*t*=1.706	0.090
Mean±SD	25.50±3.79	24.54±3.56	25.78±3.83		
cT category [*n* (%)]					
T2	13 (8.5)	3 (8.6)	10 (8.5)	χ^2=0.944	^{MC}P=0.666
T3	124 (81)	27 (77.1)	97 (82.2)		
T4	16 (10.5)	5 (14.3)	11 (9.3)		
cN category [*n* (%)]					
N0	34 (22.2)	15 (42.9)	19 (16.1)	χ^2=11.199*	0.004*
N1	85 (55.6)	14 (40)	71 (60.2)		
N2	34 (22.2)	6 (17.1)	28 (23.7)		
cTNM classification [*n* (%)]					
II	54 (35.3)	12 (34.3)	42 (35.6)	χ^2=0.020	0.887
III	99 (64.7)	23 (65.7)	76 (64.4)		
Distance AV (cm)					
Median (minimum–maximum)	7 (3–11)	7 (3–11)	7 (3–11)	*U*=2005.500	0.794
Mean±SD	7.18±2.10	7.06±2.41	7.21±2.01		
CEA (ng/ml)					
Median (minimum–maximum)	4.5 (0.02–29)	2.7 (0.05–24.5)	4.5 (0.02–29)	*U*=621.500*	<0.001*
Mean±SD	6.31±6.38	3.51±4.11	7.14±6.70		
Tumor differentiation [*n* (%)]					
Well	13 (8.5)	3 (8.6)	10 (8.5)	χ^2=0.001	1.000
Moderate	118 (77.1)	27 (77.1)	91 (77.1)		
Poor	22 (14.4)	5 (14.3)	17 (14.4)		
Tumor size (cm)					
Median (minimum–maximum)	6 (2–10)	4 (2–8)	6 (4–10)	*U*=1038.500*	<0.001*
Mean±SD	6.12±1.98	4.83±1.71	6.50±1.89		
Type of surgery [*n* (%)]					
APR	45 (29.4)	8 (22.9)	37 (31.4)	χ^2=0.939	0.333
Sphincter saving	108 (70.6)	27 (77.1)	81 (68.6)		
Time interval (days)					
Median (minimum–maximum)	50 (34–78)	60 (35–72)	45 (34–78)	*U*=1016.50*	<0.001*
Mean±SD	52.41±9.85	58.40±8.66	50.63±9.51		
Performance 0 [*n* (%)]	95 (62.1)	20 (57.1)	75 (63.6)	χ^2=0.472	0.492
Performance 1 [*n* (%)]	58 (37.9)	15 (42.9)	43 (36.4)		

χ^2, χ^2 test; CEA, carcinoembryonic antigen; MC, Monte Carlo; pCR, pathologic complete response; *t*, Student *t* test; *U*, Mann–Whitney test. *P*: *P* value for comparing between the two studied groups. *Statistically significant at *P* value less than or equal to 0.05.

undergoing drastic surgery, patients with high pCR achievement might think about local excision or the watch and wait approach. On the other hand, patients whose pCR prediction is lower may be deemed candidates for more intensive neoadjuvant treatment.

According to the study, the incidences of pCR after nCRT for rectal cancer can reach up to 25% [3,4]. Our study's sample of rectal cancer patients included 22.9% with pCR.

Still, there was no reliable clinical indicator for rectal cancer. This study, which involved 153 LARC patients, demonstrated that the likelihood of pCR for LARC patients after neoadjuvant CRT may be significantly predicted by preoperative nodal status, tumor size, the interval between neoadjuvant therapy and surgery, and serum CEA level prior to treatment.

In the current study, CEA levels less than 5 were associated with pCR rates in both univariate and multivariate analyses. Consistent with our findings,

Table 2 Univariate analysis of predictors for pathologic complete response

	pCR (*N*=35)	Non-pCR (*N*=118)	OR (LL–UL 95% CI)	*P*
Age (years)				
Minimum–maximum	26–73	26–77	0.983 (0.952–1.014)	0.273
Mean±SD	50.74±12.27	53.31±12.12		
Sex [*n* (%)]				
Male	19 (54.3)	70 (59.3)	Reference	–
Female	16 (45.7)	48 (40.7)	1.228 (0.574–2.625)	0.596
BMI (kg/m^2)				
Minimum–maximum	18–33	17–34	0.914 (0.823–1.015)	0.092
Mean±SD	24.54±3.56	25.78±3.83		
cT category [*n* (%)]				
T2	3 (8.6)	10 (8.5)	Reference	–
T3	27 (77.1)	97 (82.2)	0.925 (0.238–3.611)	0.914
T4	5 (14.3)	11 (9.3)	1.515 (0.286–8.032)	0.625
cN category [*n* (%)]				
N0	15 (42.9)	19 (16.1)	Reference	–
N1	14 (40)	71 (60.2)	0.250 (0.103–0.606)	0.002*
N2	6 (17.1)	28 (23.7)	0.271 (0.089–0.825)	0.021*
cTNM classification [*n* (%)]				
II	12 (34.3)	42 (35.6)	Reference	–
III	23 (65.7)	76 (64.4)	1.059 (0.479–2.341)	0.887
Distance AV (cm)				
Minimum–maximum	3–11	3–11	0.965 (0.805–1.157)	0.701
Mean±SD	7.06±2.41	7.21±2.01		
CEA (ng/ml) [*n* (%)]				
>5	7 (20)	62 (52.5)	Reference	–
≤5	28 (80)	56 (47.5)	3.636 (1.038–12.742)	0.044*
Tumor differentiation [*n* (%)]				
Well	3 (8.6)	10 (8.5)	Reference	–
Moderate	27 (77.1)	91 (77.1)	0.989 (0.254–3.853)	0.987
Poor	5 (14.3)	17 (14.4)	0.980 (0.192–5.007)	0.981
Tumor size (cm) [*n* (%)]				
>5	10 (28.6)	75 (63.6)	Reference	–
≤5	25 (71.4)	43 (36.4)	4.360 (1.914–9.936)	<0.001*
Type of surgery [*n* (%)]				
APR	8 (22.9)	37 (31.4)	Reference	–
Sphincter saving	27 (77.1)	81 (68.6)	1.542 (0.640–3.715)	0.335
Time interval (weeks) [*n* (%)]				
≤7	5 (14.3)	67 (56.8)	Reference	–
>7	30 (85.7)	51 (43.2)	7.882 (2.858–21.737)	<0.001*
Performance [*n* (%)]	20 (57.1)	75 (63.6)		
0	15 (42.9)	43 (36.4)	Reference	–
1	20 (57.1)	75 (63.6)	0.764 (0.355–1.647)	0.493

CEA, carcinoembryonic antigen; CI, confidence interval; LL, lower limit; OR, odd's ratio; pCR, pathologic complete response; UL, upper limit. *Statistically significant at *P* value less than or equal to 0.05.

Table 3 Multivariate analysis# of predictors for pathologic complete response

	OR	LL–UL 95% CI	*P*
cN category	0.101	0.025–0.412	0.001*
CEA (≤5) (ng/ml)	6.888	1.662–28.551	0.008*
Tumor size (≤5) (cm)	6.176	2.110–18.080	0.001*
Time interval (>7) (weeks)	39.413	8.892–174.700	<0.001*

CEA, carcinoembryonic antigen; CI, confidence interval; LL, lower limit; OR, odd's ratio; UL, upper limit. #All variables with *P* value less than 0.05 was included in the multivariate. *Statistically significant at *P* value less than or equal to 0.05.

Yeo *et al.* [15] also showed that the CEA level prior to treatment was a significant predictive predictor of pCR in a sample of 609 patients who had preoperative CRT.

Garland *et al.* [16] found that pretreatment blood CEA levels and a decline in pre-to-post-treatment serum CEA levels were independent risk factors for pCR.

Zhang *et al.* [14] found that the pretreatment CEA level was significantly greater in the non-pCR group than in the pCR group, and that this relationship was

significant between pCR and a normal pretreatment CEA level in both univariate and multivariate analyses.

Armstrong *et al.* [17] found that statin use, being close to the anal margin, and having a lower pretreatment CEA level were predictors of pCR after examining the clinical features of 885 people.

A 6–8-week interval should be provided between chemoradiation and surgery, according to Francois *et al.* [18]. This was done as opposed to a 2–3-week interval based on a statistically nonsignificant improvement in sphincter preservation rates without surgical complications.

Because of these conflicting findings, the standard treatment protocol for rectal cancer currently includes a 6–8-week interval between chemoradiation and surgery.

Extended delay between CRT completion and surgery may lead to a higher rate of progression-free radiation necrosis (pCR) and subsequent tumor regression.

The independent predictor of pCR in this trial was the time interval of more than or equal to 8 weeks between chemoradiation and surgery.

Similarly, Kalady *et al.* [19] assessed the predictors of postoperative cancer resection (pCR) in 242 patients and discovered that the only factor substantially linked with pCR was an interval greater than 8 weeks between the end of preoperative chemotherapy and radiotherapy and surgical resection.

An interval of more than 7 weeks was linked to greater pCR (28 vs. 16%, P=0.030), according to Wolthuis *et al.* [20]. Additionally, the long-interval group had a higher 5-year cancer-specific survival rate (91 vs. 83%, P=0.046) than the short-interval group.

A longer time between chemoradiation and surgery was shown to be an independent predictor of achieving a pCR by de Campos-Lobato *et al.* [21]. This investigation confirms that a longer delay is safe for patients as it does not increase perioperative or postoperative morbidity. Additionally, there was a lower rate of local recurrence after a period of time greater than or equivalent to 8 weeks.

Another clinical factor influencing pCR performance in LARC patients may be the tumor's longitudinal length, which reflects the size of the tumor.

Studying 297 LARC patients who had neoadjuvant CRT, Garland *et al.* [16] discovered that patients with smaller tumors had a higher chance of achieving pCR (5.0±2.0 vs. 6.0±2.0 cm, P=0.008). Tumor size during endoscopy was found to be an independent predictor of pCR using multivariate analysis.

In a study of 249 LARC patients, Park *et al.* [27] found that while tumor size was not a predictor of pCR, univariate analysis revealed a considerably greater proportion of pCR rate in patients with tumors less than or equal to 4 cm (37.61 vs. 18.40%, P=0.001).

Only the univariate analysis findings indicated a correlation between tumor size and pCR in the Lee *et al.* [23] study where the tumor size cut-off value was established at 5 cm, in line with Park and colleagues.

Patients with smaller tumors had a higher chance of achieving pCR, according to Russo *et al.*'s [22] univariate analysis but the study did not specify a cut-off value for grouping or perform multivariate analysis to further corroborate this finding.

In Huh *et al.*'s [24], 58-patient trial, the pCR rate was 11/25 (44%) for patients with tumors less than 5 cm, and 5/33 (15%) for those with tumors more than 5 cm. They came to the conclusion that tumor size predicts pCR independently.

Patients with longitudinal tumor lengths less than 5 cm had a higher chance of achieving pCR in this study, according to univariate and multivariate analysis, than patients with longitudinal tumor lengths greater than 5 cm.

Positive pathological nodes have been linked to a poor outcome in colorectal cancer. Higher pCR rates have been linked to pretreatment negative lymph nodes in individuals with LARC after neoadjuvant CRT.

There is not always a correlation between the pathological and clinical N stages. Current image studies may make it difficult to distinguish reactive nodes from metastatic nodes. Positive nodal status prior to therapy, however, typically indicates tumor growth and aggressiveness [25].

According to Huang *et al.* [26] just 19.3% of patients with a pretreatment positive N stage attained a pCR, compared to 39.4% of patients with a clinically negative N stage. Consequently, in our investigation, clinical non-N stage was thought to be a possible pCR indication.

These results raise the possibility that clinical node positive is a sign of a more severe illness that is less responsive to local treatment. Nonoperative therapy may have a lower chance of success for these patients. Therefore, at this point, individuals with stage III disease should be chosen very carefully for the watch-and-wait approach.

Further randomized clinical trials should be conducted in the future to determine the predictors of pCR and clarify any relevant pathways in order to resolve these contentious elements.

Total mesorectal excision may not be beneficial for patients who are thought to be good candidates for neoadjuvant CRT; instead, nonoperative care or local excision may be the best course of action for these patients.

In conclusion, this study demonstrated that a pretreatment CEA level of less than or equal to 5 ng/ml and an interval from the completion of neoadjuvant CRT to surgery of more than or equal to 8 weeks were independent clinical predictors for achieving pCR. These findings may help clinicians predict the prognosis of patients and develop individualized treatment strategies.

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Conflicts of interest
There are no conflicts of interest.

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